

ON THE ROLE OF THE US GOVERNMENT IN THE DEVELOPMENT OF NORVIR^R

My name is John Erickson. I am the President and Chief Scientific Officer of Sequoia Pharmaceuticals Inc., a small for-profit drug discovery company located in Maryland, focused on the development of new therapeutic approaches to combating drug resistant infections with an emphasis on HIV/AIDS. I am also the Founder of the Institute for Global Therapeutics, a non-profit, 501(c)(3) organization founded by my wife and I to develop safe, effective and affordable new therapeutic approaches to combating drug resistant infections, with an emphasis on HIV/AIDS, for resource-poor settings. I have been involved in HIV/AIDS drug discovery and development for most of my career, first as a researcher and project leader, later as a government laboratory director, and, most recently, as an entrepreneur-scientist, investor and fund-raiser of for-profit and non-profit drug discovery activities. Most of my drug discovery work has focused on the development of new HIV protease inhibitors such as Norvir^R.

I was a scientist at Abbott from 1985-1991, during which time I initiated a new research program to discover HIV protease inhibitors. Because we received federal funding for this program, and because this program ultimately led to the development of Norvir, I have been asked to describe the role that US government funding played in the development of Norvir. I am not here to give a learned opinion of the petition, nor on the legal aspects of the petition. I am here out of a sense of civic duty and in the spirit of Abraham Lincoln who said “If you give the people the truth, the [Re]public will be safe”. But I cannot help but take the opportunity of this forum to also comment on the larger issue of drug pricing, a powerful market force that has daily and long-term effects on drug discovery activities whether they are in profit or non-profit settings.

Now for some historical facts.

In 1988, Abbott received a grant under a federally chartered program known as the National Cooperative Drug Discovery Group for AIDS (which I will refer to as the

NCDDG program or grant). The NCDDG programs for AIDS were administered by the National Institute of Allergy and Infectious Diseases in the Department of Health and Human Services. The purpose of the NCDDG program was to promote synergy among government, industry and academic laboratories to translate basic research findings on HIV into novel antiretroviral therapies. The NCDDG-AIDS program was a response to the national health crisis that HIV/AIDS represented in the 1980's. At that time, and in sharp contrast to today, targeted antiviral research programs were largely non-existent in the pharmaceutical industry. Thus, the NCDDG program also was a tacit recognition by the government that getting the pharmaceutical industry engaged in this effort would be essential for the rapid development of new and effective antiviral drugs.

The award of the NCDDG-AIDS grant gave the HIV project a much-needed funding boost. In my opinion, it catalyzed the development of the antiviral program. I have often been asked "if not for the NCDDG grant, would Norvir exist today?" A fair question, that no one can answer with certainty. What is certainly true is that the federal grant facilitated the research that led directly to the development of Norvir. Let me explain.

As the Principal Investigator, I was responsible for the conduct of research performed under the grant. I used the funding to recruit a team of scientists to develop a new type of antiviral drug that we hoped would inhibit the spread of HIV infection by blocking a viral-encoded enzyme, called HIV protease. This was an entirely new area of research that required a critical mass of scientists from different disciplines. Without the prestige and dollars that came with the NCDDG award, it is unlikely that the HIV protease inhibitor project would have received internal funding at the time. Interest in HIV as a therapeutic area by pharmaceutical companies was the exception rather than the rule in the late 80's. The NCDDG grant gave us an opportunity to take a risk that management was not yet prepared to take on its own. The helping hand of government risk-sharing was accepted again by Abbott a few years later when it was time to take a drug candidate known as A77003 into the costly clinical development phase of research.

A77003, an early precursor of Norvir, was a highly potent inhibitor of HIV, but could not be administered in oral form. Since we had no idea whether a protease inhibitor would be effective in an HIV-infected patient, we thought it made sense to do a proof-of-concept study to test the drug's efficacy using a parenteral route of administration. However, Abbott was not ready to undertake the clinical development of A77003 because it was concerned that an intravenous compound would not generate sufficient revenue to justify the investment. When the government saw the potential benefit of our new medicine, it agreed to fully fund and to conduct the necessary pre-clinical and clinical development phases up to and through Phase II trials. Abbott agreed to manufacture and provide the necessary drug quantities for the studies. And so, in 1991, a drug development collaboration was born between Abbott, the National Cancer Institute and the National Institute for Allergies and Infectious Diseases. A77003 never made it beyond early Phase I studies; but the commitment of the government to assist Abbott in dollars and in-kind in the development of its protease inhibitor program was never in doubt.

In 1991, I was recruited to the NCI to establish a structure-based drug design research program focused on cancer and AIDS. I continued working with some of my former research team members from Abbott to understand the critical features of how symmetry-based inhibitors interacted with the target enzyme; we published several papers together during the period 1991-1994 or so. I also began a study to evaluate the resistance profile of Norvir when, around 1995, our collaboration was terminated by Abbott, due to a growing concern that the government might try to exert price controls on Norvir. The company [Abbott] worried that if the AIDS community came to perceive that the government had played a major role in the development of Norvir, that it might try to pressure the government to influence the price of Norvir downwards. This demonstrates the powerful influence that even the perception of drug price tampering by the government can have on fragile public-private partnerships.

I want to turn now to the subject of how Norvir is actually used in the fight against HIV/AIDS today. Norvir is not a typical HIV drug. In addition to its antiviral activity, Norvir has the unexpected property of inhibiting its own metabolism, which makes it stay

in circulation longer. Since it inhibits the same metabolic enzymes that are responsible for breaking down and eliminating many other drugs, including competitors' protease inhibitors, co-administration of Norvir with these drugs can lead to higher than normal blood levels and prolonged circulation half-lives. This effect is termed "pharmacokinetic boosting". Because of the boosting effect, low dose Norvir is commonly co-prescribed in all antiviral cocktails that contain a protease inhibitor. It is commonly accepted practice to prescribe Norvir as an "off label" booster with all six FDA-approved protease inhibitors. You might think from what I have said that Norvir would be the ideal protease inhibitor to take all by itself, since it effectively boosts itself. However, due to poor tolerability and adverse side effects Norvir is rarely prescribed in antiviral dosages [1200 mg/day]. Instead, it is taken in 50 or 100 mg 'baby' doses along with one of the other protease inhibitors. Abbott has replaced Norvir by a new first-line protease inhibitor, Kaletra^R, which is actually a co-formulation of low dose Norvir combined with a high dose of lopinavir, a Norvir analogue that has a superior safety profile.

So, it's important to understand that the price increase of Norvir that is at the center of today's hearing does not really affect the price of Kaletra, even though it contains Norvir. What it does affect, though, is the price of every competing protease inhibitor because they must all be taken with Norvir, which is sold separately at a price comparable to that of the active antiviral agent. The net result of the price increase is that Kaletra has gone from being one of the more expensive protease inhibitor options, before the price hike, to the least expensive protease inhibitor after the price hike. It is also one of the most effective protease inhibitors on the market today, and is responsible for helping to turn AIDS from a death sentence to a chronic, treatable disease. There are still many problems to be solved in HIV therapy, including the growing problem of drug resistant HIV infections.

I would like to turn the focus of my remaining remarks on the issue of drug prices. It is difficult to find the right balance between the interests of a private company, where success is measured primarily by revenues and share value, and the public interests of the nation, where success is measured by our personal health and well-being. This is a public policy discussion that needs to take place on national, state and local levels. My hope is

that this hearing, catalyzed by the consumer advocacy group Essential Inventions, and convened by the DHHS, will become an important component of an ongoing dialogue on how we, as a nation, deal with the health of our own people.

An important viewpoint was expressed at a meeting I attended in Malaysia earlier this year, in which Mary Robinson, former President of Ireland, stated so eloquently the case for health being a basic human right. If we as a society come to embrace the notion of health as a human right, in the same way as we view the education and welfare of our children as a basic right, then, and only then, will we begin to develop the frame of mind needed to justify directing our public funds to support the costly and high-risk, but essential, R&D required to bring new drugs to the marketplace.

To put it in other terms, if the public wants lower drug prices, the public should be willing to front the risk money for drug development. I don't think we Americans believe in free-riding, but we also don't like being taken for a ride by the rest of the industrialized world whose governments provide price protection. As long as drugs and health care services are considered to be commodities, then drug prices, like energy prices, will be driven by market forces, and may run counter to the public good.

In conclusion, I hope that this historic hearing over whether the government should exercise its statutory 'march-in' rights over Norvir will become part of a record of a thoughtful dialogue between the public and private sectors on how best to share the enormous R&D risks involved in bringing important new drugs to the nation, and eventually to the world's public health marketplaces.